300.1023US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: B. Fubara — Art Unit: 1615

Re: Application of: Chih-Ming CHEN, et al.

Serial No.: 09/726,193

Filed: November 29, 2000

For: **CONTROLLED RELEASE METFORMIN FORMULATIONS**

DECLARATION UNDER 37 CFR §1.131

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

October 1, 2003

Sir:

I, Xiu Xiu Cheng, hereby state as follows:

1. This declaration is to establish completion of the invention of this application in the United States at a date prior to March 19, 1998, that is the earliest claimed priority date of the prior art references U.S. Patent No. 6,475,521 and PCT Publication No. WO 99/47128 that were cited by the applicant.

2. I am a named inventor in the present application, U.S. Patent Application No. 09/435,576.

3. To establish the date of completion of the invention of this application the following attached document is submitted as evidence:

A letter and enclosure dated March 17, 1998 to myself, Xiu Xiu Cheng, Ph.D. of Andrx Pharmaceuticals, Inc., an inventor of the present application, parent application U.S. Serial No. 09/594,637 and grandparent application U.S. Serial No. 09/045,330. The enclosure contains a draft of the grandparent application.

4. From these documents, it can be seen that the invention of this application was made at least by the date of March 17, 1998, which is a date earlier than the earliest claimed priority date of the references.

5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Xiu Xiu Cheng — Date: 10/01/03

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March 17, 1998

VIA FACSIMILE
Xiu Xiu Cheng, Ph.D.
ANDRX Pharmaceuticals, Inc.
4001 S.W. 47th Avenue, Suite 201
Fort Lauderdale, FL 33314

Re: New United States Patent Application
for: CONTROLLED RELEASE ORAL TABLET
HAVING A UNITARY CORE
Our Reference No.: 141-152

Dear Xiu Xiu:

Thank you for your facsimile letter of March 16, 1998 regarding the draft United States Patent Application for Andrx's metformin formulation.

Pursuant to our telephone discussion, we will prepare a separate patent application for the metformin/glipizide formulation and forward a draft of this application to you shortly.

Enclosed is a revised draft application. Please note that the enclosed application incorporates the comments contained in your March 16, 1998 facsimile letter but still requires some additional information. The additional information required is:

1) FIGURE 2, a graph showing the SIF and SGF dissolution profile of Lot 297450A (Example 2 of the Application.);

2) FIGURES 4-7 which are graphs of the in vivo testing reporting in your March 16, 1998 facsimile letter;

3) the conditions under which the in vivo testing was conducted;

4) the conditions such as spray rates, temperatures and pressures use to prepare the tablets; and

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5) information on the passageway such as size.

Please review the application for accuracy and provide the missing information.

If you have any questions or require any additional information, please call.

Very truly yours,

Martin P. Endres

MPE
encl
cc: Dr. Chih-Ming Chen (w/encl.)(via facsimile)

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UNITED STATES PATENT APPLICATION OF:

Xiu Xiu Cheng

CONTROLLED RELEASE ORAL TABLET HAVING A UNITARY CORE

Please add.

Dr. Chih-Ming Cheng

Dr. Steve Jan

Dr. Joseph Chao

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CONTROLLED RELEASE ORAL TABLET HAVING A UNITARY CORE

BACKGROUND OF THE INVENTION:

The present invention relates to controlled release unit dose formulations containing an antihyperglycemic drug. More specifically, the present invention relates to an oral dosage form comprising a biguanide such as metformin or buformin or a pharmaceutically acceptable salt thereof such as metformin hydrochloride or the metformin salts described in United States Patent Nos. 3,957,853 and 4,080,472 which are incorporated herein by reference. The dosage form of the present invention can provide therapeutic levels of the antihyperglycemic drug for twelve or twenty-four hour periods. In a preferred embodiment, the dosage form will be administered once a day, ideally ~~in the morning~~ after dinner or after breakfast, and provide therapeutic levels of the drug throughout the day with peak dosage levels being obtained between 8-12 hours after administration.

In the prior art, many techniques have been used to provide controlled and extended-release pharmaceutical dosage forms in order to maintain therapeutic serum levels of medicaments and to minimize the effects of missed doses of drugs caused by a lack of patient compliance.

In the prior art are extended release tablets which have an osmotically active drug core surrounded by a semipermeable membrane. These tablets function by allowing a fluid such as gastric or intestinal fluid to permeate the coating membrane and dissolve the active ingredient so it can be released through a passageway in the coating membrane or if the active ingredient is insoluble in the permeating fluid, pushed through the passageway by an expanding agent such as a hydrogel. Some representative examples of these osmotic tablet systems can be found in United States Patent Nos. 3,845,770, 3,916,899, 4,034,758, 4,077,407 and 4,783,337. United States Patent No. 3,952,741 teaches an osmotic device wherein the active agent is released from a core surrounded by a semipermeable

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membrane only after sufficient pressure has developed within the membrene to burst or rupture the membrane at a weak portion of the membrane.

The basic osmotic device described in the above cited patents have been refined over time in an effort to provide greater control of the release of the active ingredient. For example United States Patent Nos. 4,777,049 and 4,851,229 describe an osmotic dosage form comprising a semipermeable wall surrounding a core. The core contains an active ingredient and a modulating agent wherein the modulating agent causes the active ingredient to be released through a passageway in the semipermeable membrane in a pulsed manner. Further refinements have included modifications to the semipermeable membrane surrounding the active core such as varying the proportions of the components that form the membrane, i.e United States Patent Nos. 5,178,867, 4,587,117 and 4,522,625 or increasing the number of coatings surrounding the active core, i.e 5,550,170 and 4,892,729.

Although vast amounts of research have been performed on controlled or sustained release compositions and in particular osmotic dosage forms, very little research has been performed in the area of controlled or sustained release compositions that employ antihyperglycemic drugs.

The limited work on controlled or sustained release formulations that employ antihyperglycemic drugs such as metformin hydrochloride has been limited to the combination of the antihyperglycemic drug and an expanding or gelling agent to control the release of the drug from the dosage form. This limited research is exemplified by the teachings of WO 96/09293 and by the GLUCOPHAGE® product which is a commercially available product from Bristol-Myers Squibb Co. containing metformin HCl.

It is an object of the present invention to provide a controlled or sustained release formulation for an

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antihyperglycemic drug that does not employ an expanding gel forming material.

It is a further object of the present invention to provide a controlled or sustained release formulation for an antihyperglycemic drug that can provide continuous and non-pulsating therapeutic levels of an antihyperglycemic drug to an animal (or human) in need of such treatment over a twelve hour (to) twenty-four hour period.

It is a further object of the present invention to provide a controlled or sustained release formulation for an antihyperglycemic drug that obtains peak dosage levels approximately 8-12 hours after administration.

It is also an object of this invention to provide a controlled or sustained release pharmaceutical tablet having only a homogeneous osmotic core wherein the osmotic core component may be made using ordinary tablet compression techniques.

SUMMARY OF THE INVENTION

The foregoing objectives are met by a controlled release dosage form which comprises:

(a) a core which comprises:

(i) an antihyperglycemic drug;

(ii) a binding agent; and

(iii) an absorption enhancer;

(b) a semipermeable membrane coating surrounding the core; and

(c) at least one passageway in the semipermeable membrane ~~to allow release of the antihyperglycemic drug~~.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph which depicts the dissolution profile in simulated intestinal fluid ~~(SIF)~~ (pH 7.5 phospahte buffer) and simulated gastric fluid (SGF) of the formulation described in Example 1 as tested according to

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the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm.

FIG. 2 is a graph which depicts the dissolution profile in simulated intestinal fluid ~~(SIF)~~ (pH 7.5 phospahte buffer) and simulated gastric fluid (SGF) ~~of~~ the formulation described in Example 2 as tested acoording to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm.

FIG. 3 is a graph which depicts the dissolution profile in simulated intestinal fluid ~~(SIF)~~ (pH 7.5 phospahte buffer) and simulated gastric fluid (SGF) of the formulation described in Example 3 as tested according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm.

FIG. 4 is a graph depicting the in vivo dissolution profile of the formulation described in Example 1 under fasting conditions.

FIG. 5 is a graph depicting the in vivo dissolution profile of the formulation described in Example 2 under fasting conditions.

FIG. 6 is a graph depicting the in vivo dissolution profile of the formulation described in Example 3 under fed conditions (after breakfast)

FIG. 7 is a graph depicting the in vivo dissolution profile of the formulation described in Example 3 under fed conditions (after dinner)

DETAILED DESCRIPTION OF THE INVENTION

The term antihyperglycemic drugs as used this specification refers to drugs that are useful in controlling or managing noninsulin-dependent diabetes mellitus (NIDDM). Preferably the antihyperglycemic drug is a biguanide such as metformin or buformin or a pharmaceutically acceptable salt thereof such as metformin hydrochloride. ~~The antihyperglycemic drug should be freely soluble in water. The phrase freely soluble in water~~

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~~soluble includes those substances which are soluble at level of one part of solute to 3 parts of water or less.~~

The binders may be any conventionally known pharmaceutically acceptable binder ~~but it is preferred that the binder be water soluble~~ such as polyvinyl pyrrolidone ~~having a weight average molecular weight of 25,000 to 3,000,000. Other pharmaceutically acceptable water soluble polymers include~~ hydroxypropyl cellulose, hydroxyethyl cellulose, ~~and the like. Mixtures of the water soluble binders may also be used.~~ The ~~water soluble~~ binders comprise approximately about 0 to about 40% of the total weight of the core and preferably about 2-15% of the total weight of the core.

The absorption enhancer employed in the core can be any type of absorption enhancer commonly known in the art such as a fatty acid, a surfactant, a chelating agent, a bile salt or mixtures thereof. Examples of some preferred absorption enhancers are fatty acids such as capric acid, oleic acid and their monoglycerides, surfactants, ~~especially alkyl sulfates~~ such as sodium lauryl sulfate, ~~sodium dodecyl sulfate~~ and polysorbate 80, chelating agents such as citric acid and phytic acid. The core comprises approximately 1 to about 20% absorption enhancer based on the total weight of the core and most preferably about 2 to about 10% of the total weight of the core.

The core of the present invention which comprises the antihyperglycemic drug, the binder which preferably is a pharmaceutically acceptable water soluble polymer and the absorption enhancer is preferably formed by ~~mixing and tableting techniques commonly known in the art. The core may also be formed by~~ granulating the core ingredients and compressing the granules into a tablet. ~~The tableting can be performed~~ on a rotary press. Other commonly known excipients may also be included into the core such as lubricants, pigments or dyes.

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The homogeneous core is subsequently coated with a semipermeable membrane, preferably a modified polymeric membrane to form the controlled release tablet of the invention. ~~The semipermeable membrane is permeable to the passage of an external fluid such as water and biological fluids and is impermeable to the passage of the antihyperglycemic drug in the core.~~ Materials that are useful in forming the semipermeable membrane are cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate, and cellulose acetate butyrate. Other suitable polymers are described in United States Patent Nos. 3,845,770, 3,916,899, 4,008,719, 4,036,226 and 4,11210 which are incorporated herein by reference. The most preferred semipermeable membrane material is cellulose acetate comprising an acetyl content of 39.3 to 40.3%, commercially available under the tradename CA 398-10 or CA 398-3 from Eastman Fine Chemicals.

In an alternative embodiment, the semipermeable membrane can be formed from the above-described polymers and a flux enhancing agent. The flux enhancing agent increase the volume of fluid imbibed into the core to enable the dosage form to dispense substantially all of the antihyperglycemic drug through both the passageway and the porous membrane. The flux enhancing agent is a water soluble component such as sodium chloride, potassium chloride, sorbitol, mannitol, polyethylene glycol ~~(weight average molecular weight 200-1301)~~, propylene glycol, hydroxypropyl cellulose, hydroxypropyl methycellulose and mixtures thereof. The preferred flux enhancer is PEG 400.

The flux enhancing agent comprises approximately 0 to ~~25%~~ 40 of the total weight of the coating, most preferably 2-15% of the total weight of the coating. The flux enhancing agent dissolves or leaches from the semipermeable membrane

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to form paths in the semipermeable membrane for the fluid to enter the core and dissolve the active ingredient.

The semipermeable membrane may also be formed with commonly known excipients such a plasticizer. Some commonly known plasticizers include adipate, azelate, benzoate, citrate, stearate, isoebucate, sebacate, triethyl citrate, tri-n-butyl citrate, acetyl tri-n-butyl citrate, citric acid esters, and those described in the Encyclopedia of Polymer Science and Technology, Vol. 10 (1969), published by John Wiley & Sons. The preferred plasticizer is triacetin but materials such as acetylated monoglyceride, rape seed oil, olive oil, sesame oil, acetyltributylcitrate, acetyltriethylcitrate, glycerin sorbitol, diethyloxalate, diethylmalate, diethylfumarate, dibutylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacate, triethylcitrate, tributylcitrate, glyceroltributyrate, and the like. Depending on the particular plasticizer, amounts of from 0% to 60%, and preferably 2 to 20% of the plasticizer can be used based upon the total weight of the coating.

As used herein the term passageway includes an aperture, orifice, bore, hole, weaken area or an erodible element such as a gelatin plug that erodes to form an osmotic passage way for the release of the dissolved antihyperglycemic drug from the dosage form. A detailed description of the passageway can be found in United States patents such as 3,845,770, 3,916,899, 4,034,758, 4,077,407, 4,783,337 and 5,071,607.

Generally, the membrane coating around the core will comprise from about 1 to 5% and preferably about 2-3% based on the total weight of the core and coating.

In a preferred embodiment the dosage form will have the following composition:

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	Preferred	Most Preferred
CORE:		
drug	50-98%	75-95%
binder	0-40%	3-15%
absorption enhancer	1-20%	2-10%
COATING:		
semipermeable polymer	50-99%	75-95%
flux enhancer	0-25%	2-15%
plasticizer	0-48%	2-20%

The dosage forms prepared according to the present invention should exhibit the following dissolution profile when tested in a USP type 2 apparatus at 75 rpms in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37°C:

Time (hours)	Preferred	Most Preferred
2	0-25%	0-15%
4	10-45%	20-40%
8	30-90%	45-90%
12	NTL 50%	NTL 60%
16	NTL 60%	NTL 70%
20	NTL 70%	NTL 80%

NTL = NOT LESS THAN

In the preparation of the tablets of the invention, various conventional well known solvents may be used to prepare the granules and apply the external coating to the tablets of the invention. In addition, various diluents, excipients, lubricants, dyes, pigments, dispersants etc. which are disclosed in Remington's Pharmaceutical Sciences, 1995 Edition may be used to optimize the formulations of the invention. In the alternative, dry granulation techniques may be used to prepare formulation for making compressed tablets.

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DESCRIPTION OF THE PREFERRED EMBODIMENTS

EXAMPLE 1

A once a day controlled release tablet containing 850 mg of metformin HCL and having the following formula are prepared as follows:

I Core	
metformin HCl	90.54%
povidone[1], USP	4.35%
sodium tribasic phospahate	4.58%
magnesium stearate	0.5%

[1]approximate molecular weight = 50,000; dynamic viscosity (10%w/v solution at 20°C) = 5.5-8.5 m Pa s.

(a) Granulation

The metformin HCL is delumped by passing it through a 40 mesh screen and collect in a clean, polyethylene-lined container. The povidone, K-30, and sodium tribasic phosphate are dissolved in purified water. The delumped metformin HCl is then added to a top-spray fluidized bed granulator and granulated by spraying ~~with~~ the binding solution of povidone and sodium tribasic phosphate under the following conditions: ~~°C, pressure, spray rate,~~ humidity ~~bowl~~ inlet air temperature 50 – 70°C, ~~spray rate~~ 10 – 100 ml/min (depending on batch size ~~of metformin HCl granules~~). Once the binding solution is depleted, ~~and the granules are formed,~~ the granules are passed through a Comil equipped with the equivalent of an 18 mesh screen.

(b) Tabletting

The magnesium stearate is passed through a 40 mesh stainless steel screen and blended with the metformin HCl granules for approximately five (5) minutes. After blending, the ~~coated~~ granules are compressed on a rotary press fitted with 15/32" round standard concave punches (plain lower punch, upper punch with a _____ indentation pin).

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(c) Seal Coating (optional)

The ~~tablets or core~~ core tablet is seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably Opadry clear in purified water. The Opadry solution is then sprayed onto the tablet ~~or~~ core using a pan coater under the following conditions: Exhaust air temperature : 38 ~ 42°C
Atomization pressure : 20 ~ 40 psi
Spray rate : 10 ~ 15 ml/min

II Sustained Release Coating

cellulose acetate (398-10)[2]	85%
triacetin	5%
PEG 400	10%

[2] acetyl content 39.3 - 40.3%

(d) Sustained Release Coating

The cellulose acetate is dissolved in acetone while stirring with a homogenizer. The polyethylene glycol 400 and triacetin are added to the cellulose acetate solution and stirred until a clear solution is obtained. The clear coating solution is then sprayed onto the seal coated tablets in a fluidized bed coater employing the following conditions : Product temperature : 16 ~ 22°C
Atomization pressure : 3 bar Spray rate 100 ~ 150 ml/min until a theoretical coating level of approximately 3% is obtained.

The resulting tablet is tested in simulated intestinal fluid (pH 7.5) and simulated gastric fluid (SGF) according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm and found to have the following release profile:

TIME (hours)	% Released (SGF)	% Released (pH 7.5)
2	9	12
4	27	32
8	62	82
12	82	100
16	88	105
20	92	108

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The release profile in SGF and SIF of the sustained release product prepared in this Example is shown in Figure 1.

The in vivo testing of the sustained release product prepared in this Example was performed under the following conditions: _____. Figure 4 depicts the results of the in vitro testing wherein the Cmax is 0.120 and the AUC (0-t) is 0.202.

EXAMPLE 2

A controlled release tablet containing 850 mg of metformin HCL and having the following formula are prepared as follows:

I	Core
metformin HCl	88.555%
povidone[3], USP	6.368%
sodium lauryl sulfate	4.577%
magnesium stearate	0.5%

[3] approximate molecular weight = 1,000,000, dynamic viscosity (10%w/v solution at 20°C) = 300-700 m Pa s.

(a) Granulation

The metformin HCL ~~is~~ are delumped by passing it through a 40 mesh screen and collect in a clean, polyethylene-lined container. The povidone, K-90F, ~~and sodium lauryl sulfate~~ are dissolved in purified water. The delumped metformin HCl is then added to a top-spray fluidized bed granulator and granulated by spraying with the binding solution of povidone ~~and sodium lauryl sulfate~~ under the following conditions ~~Inlet air temperature, spray rate, humidity~~ _____. Once the binding solution is depleted, ~~and the metformin granules are formed,~~ the granules are passed through a Comil equipped with the equivalent of an 18 mesh screen.

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(b) Tabletting

The magnesium stearate is passed through a 40 mesh stainless steel screen and blended with the metformin HCl granules for approximately five (5) minutes. After blending, the coated granules are compressed on a rotary press fitted with 15/32" round standard concave punches (plain lower punch, upper punch with a _____ indentation pin).

(c) Seal Coating (optional)

The ~~tablet or~~ core folder core is seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably Opadry clear in purfied water. The Opadry solution is then sprayed on the core tablet ~~tablet or core~~ using a pan coater under the following conditions: Exhaust air temperature : 35 ~ 45 °C
Atomization pressure : 25 ~ 40 psi
Spray rate : 10 ~ 15 ml/min

II Sustained Release Coating

cellulose acetate (398-$\frac{1}{10}$)	85%
triacetin	5%
PEG 400	10%

Acetyl content 39.3 - 40.3%

(d) Sustained Release Coating

The cellulose acetate is dissolved in acetone while stirring with a homogenizer. The polyethylene glycol 400 and triacetin are added to the cellulose acetate solution and stirred until a clear solution is obtained. The clear coating solution is then sprayed onto the seal coated tablets in a fluidized bed coater employing the following conditions: Product temperature : 16 ~ 22 °C
Atomization pressure : 3 bar
Spray rate : 120 ~ 150 ml/min until a theoretical coating level of approximately 3% is obtained.

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The resulting tablet is tested in simulated intestinal fluid (pH 7.5) and simulated gastric fluid (SGF) according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm and found to have the following release profile:

TIME (hours)	% Released (SGF)	% Released (pH 7.5)
2	13	12
4	29	27
8	55	52
12	72	71
16	81	83
20	87	91

The release profile in SGF and SIF of the sustained release product prepared in this Example is shown in Figure 2.

The in vivo testing of the sustained release product prepared in this Example was performed under the following conditions: _____. Figure 5 depicts the results of the in ~~vivo~~ vivo fasting conditions wherein the Cmax is 0.214 and the AUC (0-t) is 0.369. ~~Figure 6 depicts the results of the in vivo fed conditions wherein the Cmax is 0.309 and the AUC (0-t) is 5.6.30.~~

EXAMPLE 3

A controlled release tablet containing 850 mg of metformin HCL and having the ~~following~~ same formula ~~are prepared~~ as in Example 2 except that an additional hole was drilled on the plain side of the coated tablet.

The resulting tablet is tested in simulated intestinal fluid (pH 7.5) and simulated gastric fluid (SGF) according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm and found to have the following release profile:

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TIME (hours)	% Released (SGF)	% Released (pH 7.5)
2	13	14
4	27	28
8	50	63
12	67	84
16	84	95
20	97	102

The release profile in SGF and SIF of the sustained release product prepared in this Example is shown in Figure 3.

The in vivo testing of the sustained release product prepared in this Example was performed under the following conditions: _____. Figure 7 depicts the results of the in ~~vivo~~ vitro fed conditions wherein the Cmax after breakfast is 0.528 and the AUC (0-t) is ~~0.799~~ 0.707, while the Cmax after dinner is 0.751 and the AUC (0-t) is 0.659.

While certain preferred and alternative embodiments of the invention have been set forth for purposes of disclosing the invention, modifications to the disclosed embodiments may occur to those who are skilled in the art. Accordingly, the appended claims are intended to cover all embodiments of the invention and modifications thereof which do not depart from the spirit and scope of the invention.

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We claim:

1. A controlled release antihyperglycemic tablet which comprises:

(a) a core consisting essentially of
(i) an antihyperglycemic drug;
(ii) a binding agent; and
(iii) an absorption enhancer; and

(b) a semipermeable membrane coating covering said core; and

(c) at least one passageway in the semipermeable membrane ~~to allow the release of the antihyperglycemic drug from the core to the environment of use.~~

2. A controlled release pharmaceutical tablet as defined in claim 1 wherein the antihyperglycemic drug is a biguanide.

3. A controlled release pharmaceutical tablet as defined in claim 2 wherein the antihyperglycemic drug is metformin or a pharmaceutically acceptable salt thereof.

4. A controlled release pharmaceutical tablet as defined in claim 2 wherein the antihyperglycemic drug is buformin or a pharmaceutically acceptable salt thereof.

5. A controlled release pharmaceutical tablet as defined in claim 1 wherein the binding agent ~~is water soluble.~~ see page 5 DC 6/98.

6. A controlled release pharmaceutical tablet as defined in claim 5 wherein the water soluble binding agent is polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxyethyl cellose or mixtures thereof.

hydroxypropyl methylcellulose

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7. A controlled release pharmaceutical tablet as defined in claim 6 wherein the water soluble binding agent is polyvinyl pyrrolidone.

8. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is selected from the group consisting of fatty acids, surfactants, chelating agents, bile salts or mixtures thereof. phe

9. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is a fatty acid selected from the group consisting of capric acid, oleic acid or their monoglycerides.

10. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is a surfactant selected from the group consisting of sodium lauryl sulfate, ~~sodium dodecyl sulfate~~ sodium taurocholate and polysorbate 80.

11. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is a chelating agent selected from the group consisting of citric acid and ~~phytic acid~~. EDTA and EGTA. phytic ac

12. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is a bile salt.

13. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is sodium lauryl sulfate.

~~14. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is sodium tribasic phosphate.~~

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15. A controlled release pharmaceutical tablet as defined in claim 1 wherein the semipermeable membrane around the core is a water insoluble cellulose derivative.

16. A controlled release pharmaceutical tablet as defined in claim 15 wherein the water insoluble cellulose derivative in the membrane around the core is cellulose acetate.

17. A controlled release pharmaceutical tablet as defined in claim 1 wherein semipermeable membrane comprises a flux enhancer.

18. A controlled release pharmaceutical tablet as defined in claim 17 wherein the flux enhancer is sodium chloride, potassium chloride, sorbitol, mannitol, polyethylene glycol, propylene glycol, hydroxypropyl cellulose or mixtures thereof.

19. A controlled release pharmaceutical tablet as defined in claim 18 wherein the flux enhancer is polyethylene glycol with an average molecular weight between 380 and 420.

20. A controlled release pharmaceutical tablet as defined in claim 1 wherein the semipermeable membrane comprises a plasticizer.

21. A controlled release pharmaceutical tablet as defined in claim 20 wherein the plasticizer is triacetin.

22. A controlled release pharmaceutical tablet as defined in claim 1 wherein at least ~~two~~ one passageway ~~are~~ is formed in the semipermeable memorane.

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23. A controlled release pharmaceutical tablet as defined in claim 1 wherein the peak ~~dosage~~ plasma level is obtained 8-12 hours after administration.

24. A controlled release antihyperglycemic tablet which consisting essentially of:

(a) a core consisting essentially of:

(i) metformin or a pharmaceutically acceptable salt thereof;

(ii) polyvinyl pyrrolidone; and

(iii) sodium lauryl sulfate; and

(b) a semipermeable membrane coating covering said core comprising:

(i) cellulose acetate;

(ii) polyethylene glycol with an average molecular weight between 380 and 420; and

(iii) a plasticizer; and

(c) at least one passageway in the semipermeable membrane ~~to allow the release of the antihyperglycemic drug from the~~ core to the environment of use.

(d) optional IR loading

25. A controlled release pharmaceutical tablet as defined in claim 24 wherein the peak ~~dosage level~~ is obtained 8-12 hours after administration. plasma level

26. Dosing time

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ABSTRACT

A controlled release antihyperglycemic tablet that does not contain an expanding or gelling polymer and comprising a core containing the antihyperglycemic drug, a semipermeable membrane coating the core and at least one passageway in the membrane to allow the drug to be released from the core.